

UNITED STATES AIR FORCE IERA

Real-Time Breath Analysis of Vapor Phase Uptake of 1,1,1-Trichloroethane Through the Forearm

Sidney M. Gordon

Battelle Corporation
505 King Avenue
Columbus, OH 43201-2693

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Institute for Environment, Safety and
Occupational Health Risk Analysis
Risk Analysis Directorate
Risk Assessment Division
2513 Kennedy Circle
Brooks Air Force Base TX 78235-5123

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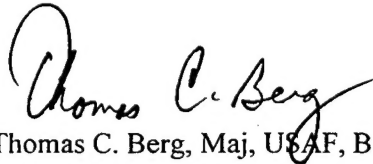
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Thomas C. Berg, Maj, USAF, BSC
Chief, Environmental Sciences



Kenneth L. Cox, Lt Col, USAF, MC,SFS
Chief, Risk Assessment Division

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Executive Summary

This study was conducted using newly-developed breath monitoring technology to determine the vapor phase uptake by humans of 1,1,1-trichloroethane by dermal absorption under exposure conditions that may reasonably be encountered by U.S. Air Force or other workers performing similar operations. Levels of 1,1,1-trichloroethane were monitored continuously in real time as dermal vapor exposure to the chemical took place following pre-conditioning of the exposed skin in heated saline solution, heated tap water, or heated room air.

The study showed that normal untreated skin provides an excellent barrier to the dermal uptake of a solvent vapor such as 1,1,1-trichloroethane. Warm and/or moist skin, on the other hand, was found to promote skin permeability to 1,1,1-trichloroethane vapors. The study also showed a strong linear dependence of exhaled breath concentration on 1,1,1-trichloroethane vapor concentration at 40°C, following skin pre-conditioning in physiological saline solution at 40°C for a period of 15 min. This indicates that, over the exposure range used (~1,200—4,800 mg/m³), dermal uptake is a direct function of vapor concentration.

Further investigation showed that, for a fixed solvent vapor concentration, vapor temperature, and pre-conditioning temperature, the exhaled breath concentration is essentially independent of the specific soak medium used (saline, tap water, or room air), at the vapor and soak temperatures used. In one of the early test experiments conducted, the soak medium (room air) was held at room temperature (~25°C) and no clear increase in breath concentration was observed. However, for soak-medium temperatures between 30 and 40°C, the breath concentration was largely unaffected by soak-medium temperature, for a fixed solvent vapor concentration, vapor temperature, and soak medium (saline).

Measurements of dermal uptake of 1,1,1-trichloroethane vapors were compared with predicted contributions of inhalation uptake, under the same experimental conditions, using the results of a recently-reported chamber inhalation study. From these estimates, dermal uptake (from assumed exposure over 30% of the total body surface area) as a fraction of inhalation exposure (in the absence of any respiratory protection) is an average of $0.031 \pm 0.005\%$. This suggests that the

contribution of dermal uptake of 1,1,1-trichloroethane vapors to total absorbed dose is negligible compared with the inhalation component.

SECTION 1.0 — Objective

The purpose of this study was to use newly-developed breath monitoring technology to determine the vapor phase uptake by humans of 1,1,1-trichloroethane by dermal absorption under exposure conditions that may reasonably be encountered by U.S. Air Force or other workers performing similar operations. Levels of 1,1,1-trichloroethane were monitored continuously in real time as dermal vapor exposure to the chemical took place, and the results were used to estimate the total absorbed dose by inhalation, ingestion, and vapor phase dermal uptake for a simulated 8-hr occupational exposure.

SECTION 2.0 — Background

The absorption via the skin of certain chemicals as either liquids or solids is well established (Grandjean, 1990). There have, however, been far fewer studies of dermal absorption from the vapor phase, and it has long been assumed that such absorption is insignificant compared to uptake by inhalation (Riihimäki and Pfäffli, 1978; McDougal et al., 1986; McDougal et al., 1990; Corley et al., 1997). Riihimäki and Pfäffli (1978) used human volunteers to demonstrate the dermal uptake of several solvent vapors including toluene and xylene. More recently, Johanson and Boman (1991) and Corley et al. (1997) exposed human volunteers to vapors of the widely used glycol ether solvent, 2-butoxyethanol, and measured the concentration of the solvent in blood samples to determine the dermal uptake. In the largest study of its kind, Brooke et al. (1998) exposed groups of human volunteers to a range of substances (xylene, toluene, tetrahydrofuran, methyl ethyl ketone, and 1-methoxypropan-2-ol), either “whole body” or via the skin only. Uptake after exposure was determined by monitoring the parent compound or metabolite in blood, urine, or single breath. Their study indicated that uptake of vapors via the skin can occur, but for some chemicals, such as xylene, toluene, and tetrahydrofuran, this contributes little to the overall body burden. For other substances, such as the glycol ethers, dermal absorption from the vapor phase may be an important contributor to total uptake, especially in situations where protective equipment is used to limit inhalation exposure.

Occupational exposure to high concentrations of organic chemicals, such as solvents and jet fuels, is of concern to the United States Air Force (USAF) because of various activities at Air Force bases (e.g., degreasing, refueling, fire-fighting) and National Priority List hazardous waste sites that can result in significant uptake of these chemicals by inhalation or dermal absorption. Direct inhalation of the vapors is largely avoided by requiring workers to wear respirators. Similarly, direct dermal absorption of liquid solvents through the skin is limited by using protective gloves. However, the atmosphere in these work areas frequently contains high vapor concentrations of the chemicals, and percutaneous absorption of these vapors can occur. The extent, if any, of vapor penetration of unprotected skin by the chemicals widely used by the Air Force is not generally known. As a result, exposure and the corresponding body burdens cannot

be assessed for these exposure scenarios, and estimates of the associated health risks are speculative at best.

Because of the dynamic equilibrium between the concentration of a volatile organic compound (VOC) in the blood and its concentration in exhaled breath (Wallace et al., 1996), breath measurements can be used to estimate body burden and to detect changes in body burden with time (Weisel et al., 1992; Raymer et al., 1991; Gordon et al., 1992; Wallace et al., 1993; Gordon et al., 1998). Several studies based on exhaled breath analysis have shown that significant dermal exposure to chloroform occurs while showering or bathing, and the dose is roughly comparable to that resulting from inhalation (Jo et al., 1990; Andelman, 1985; Weisel and Jo, 1996; Wester, and Maibach, 1994). In a recently completed study, Gordon et al. (1998) used newly-developed breath monitoring technology to show that dermal-only absorption of chloroform while bathing is strongly dependent on water temperature, with subjects at the highest temperatures (40°C) exhaling about 30 times more chloroform than the same subjects at the lowest temperatures (30°C).

The purpose of this study was to use this breath monitoring technique (Gordon et al., 1998) to determine the vapor phase uptake by humans of 1,1,1-trichloroethane via dermal absorption under exposure conditions and at temperatures that may reasonably be encountered by USAF or other workers performing similar operations. Levels of 1,1,1-trichloroethane were monitored continuously in real time as dermal vapor exposure to the chemical took place, and the results were used to estimate the contributions of inhalation and vapor phase dermal uptake to the total absorbed dose for a typical occupational exposure.

SECTION 3.0 — Experimental Methods

The experimental procedures employed to determine dermal-only absorption of solvent vapors by human volunteers were based on the methods that were used in a previous study to evaluate the effect of water temperature on dermal-only exposure to chloroform (Gordon et al., 1998). Subjects were exposed to the solvent 1,1,1-trichloroethane via the skin while breathing pure air through a face mask. Their exhaled breath was delivered to a glow discharge source/ion trap mass spectrometer that allowed continuous real-time measurements of 1,1,1-trichloroethane in the breath. The method is particularly well suited to studying dermal exposure because the full face mask eliminates inadvertent exposure to contaminated air.

3.1 Exposure Conditions and Breath Sampling Protocol

Experiments were conducted with four human volunteers. Each subject exposed an arm in a small chamber to known vapor concentrations of 1,1,1-trichloroethane at a fixed temperature (40°C) for ~25 min and the resulting breath levels of the chemical were measured in real time. To ensure that there was no inadvertent exposure to any 1,1,1-trichloroethane in the room air, each subject was fitted with a full face mask that was attached to a purified air supply. The subject inhaled clean air through the first one-way valve and exhaled through the second valve into the mixing chamber of the breath inlet system. Before each experiment, the fit of the mask was checked for leak tightness using two methods: (1) the subject was exposed to isoamyl acetate ("banana oil") and asked if he/she could detect any odor; and (2) the pre-exposure signal response for 1,1,1-trichloroethane in the subject's breath was compared with the signal due to zero-grade air in the analyzer.

Because of the potential effect of skin moisture on dermal absorption (Meuling et al., 1997), each subject was required to soak the forearm and hand in various soak media at different temperatures prior to exposure to the 1,1,1-trichloroethane vapor. Information on the subjects and the conditions in each experiment are provided in Table 3-1. The study protocol was

Table 3-1. Subject Characteristics and Experimental Conditions

Subject	Expt. No.	Sex	Age	Ht (m)	Wt (kg)	Target Vapor Conc. (mg/m ³)	Actual Vapor Conc. (mg/m ³) ±SD ^a	Vapor Conc. (TLV) ^b	Vapor Temp. (°C)	Soak Medium	Soak Temp. (°C)
1	1	M	25	1.89	95.7	955 ^c	1,205 ^e	0.63	40	Saline	40
	2					1,910 ^d	1,878 ±114	0.98	40	Saline	40
	3					1,910	2,118 ±107	1.11	40	Tap Water	40
	4					1,910	2,083 ±114	1.09	40	Room Air	40
2	5	F	38	1.88	69.9	955	1,227 ±52	0.64	40	Saline	40
	6					1,910	2,148 ±97	1.12	40	Saline	40
	7					1,910	2,361 ±111	1.24	40	Tap Water	40
	8					1,910	2,031 ±212	1.06	40	Room Air	40
3 ^f	9	M	42	1.83	72.6	1,910	2,102 ±59	1.10	40	Saline	30
	10					1,910	2,160 ±82	1.13	40	Saline	35
4	11	F	23	1.60	74.8	1,910	2,238 ±106	1.17	40	Saline	30
	12					1,910	2,407 ±135	1.26	40	Saline	35
Test Subject 1	—	M				4,775 ^g	~4,860	~2.6	40	Saline	40
Test Subject 2	—	M				4,775	~4,860	~2.6	40	Room Air	~25

^a SD = standard deviation.^b Threshold Limit Value (TLV) is 1,910 mg/m³ (= 353.8 ppm) for 1,1,1-trichloroethane (ACGIH, 1997).^c 0.5 x TLV.^d 1.0 x TLV.^e Average of two measurements; all other values are average of three or four measurements.^f Data rejected from this subject; erratic breathing pattern.^g 2.5 x TLV.

reviewed and approved by the Battelle Human Subjects Committee, and informed consent was obtained from each subject.

Forearm-and-hand-only exposures were conducted in a small (65.7 L) Plexiglas chamber equipped with a sealed entry port for the arm. The entry port consists of a silicone rubber iris collar through which the subject presses his/her hand so that the entire forearm and hand are contained in the chamber. Chamber temperature and humidity are recorded with a digital thermometer (Model 52; Fluke Corp., Everett, WA) and hygrometer (Omega Model CT485B), and a muffin fan ensures that the vapor is thoroughly mixed. An electrically-controlled thermal injector block from an old gas chromatograph was placed in a corner of the chamber and was used to adjust the temperature of the chamber atmosphere to 40°C.

Test atmospheres were generated by injecting aliquots of pure 1,1,1-trichloroethane via a septum onto the surface of the injector block to vaporize the chemical directly into the humidified, ultra-high purity air in the chamber. The concentration of 1,1,1-trichloroethane in the chamber air was analyzed using a gas chromatograph with flame ionization detector. Vapor concentrations used in the experiments are summarized in Table 3-1.

Upon entering the test laboratory, the subject first conditioned his/her forearm and hand to be used for exposure by soaking them, at fixed temperatures between 25 and 40°C for ~15 min, in a bucket containing either physiological saline (0.9% sodium chloride solution) or tap water, or by wrapping them in an electric heating pad to condition them in dry room air. At the end of the conditioning period, the subject put on the face mask and, after the outlet tube from the face mask was attached to the real-time breath analyzer, he/she provided a brief pre-exposure breath sample. Then, the subject inserted his/her forearm and hand into the chamber, after which a small volume (50 μ L) of 1,1,1-trichloroethane was slowly injected onto the heating block to vaporize the compound. Breath measurements of 1,1,1-trichloroethane were made every 6 s while the subject continued to breathe purified air. After 15-40 min, when the real-time breath analyzer indicated that the breath 1,1,1-trichloroethane level was at, or close to, a plateau, the subject withdrew his/her forearm and hand from the chamber. Post-exposure breath measurements were taken for a further 30 min before the subject was allowed to remove the face



Figure 3-1. Photograph showing subject with arm inserted into Plexiglas chamber containing solvent vapor. Subject is fitted with face mask, one side of which is attached to purified air supply; outlet carries exhaled breath sample to real-time breath analyzer.

mask. Figure 3-1 shows the chamber and real-time breath analyzer setup with a subject providing a breath sample.

3.2 Breath Analysis

The real-time breath analyzer (Gordon et al., 1998), shown schematically in Figure 3-2, consists of a breath inlet unit, a direct breath sampling interface, and an ion trap mass spectrometer (ITMS). Figure 3-3 shows the breath inlet attached to the analytical system (Gordon et al., 1992;

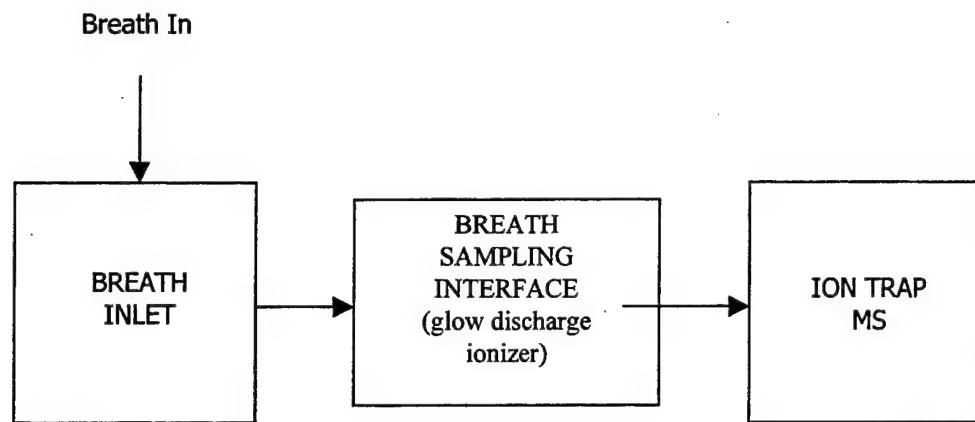


Figure 3-2. Major components of the continuous real-time breath analyzer.

Kelly et al., 1991). For all of the breath measurements, a face mask (Model 8932, Hans Rudolph, Inc., Kansas City, MO), equipped with a 2-way non-rebreathing valve set, was attached to the breath inlet to isolate the subject from any 1,1,1-trichloroethane in the room air. The inlet valve of the face mask was connected to a cylinder containing hospital-grade breathing air. The exhaust valve of the face mask was connected to the breath inlet. The breath sample is vacuum-extracted at a constant rate from the breath inlet volume by the vacuum in the direct breath sampling interface and flows into the ion trap without any attention from the subject.

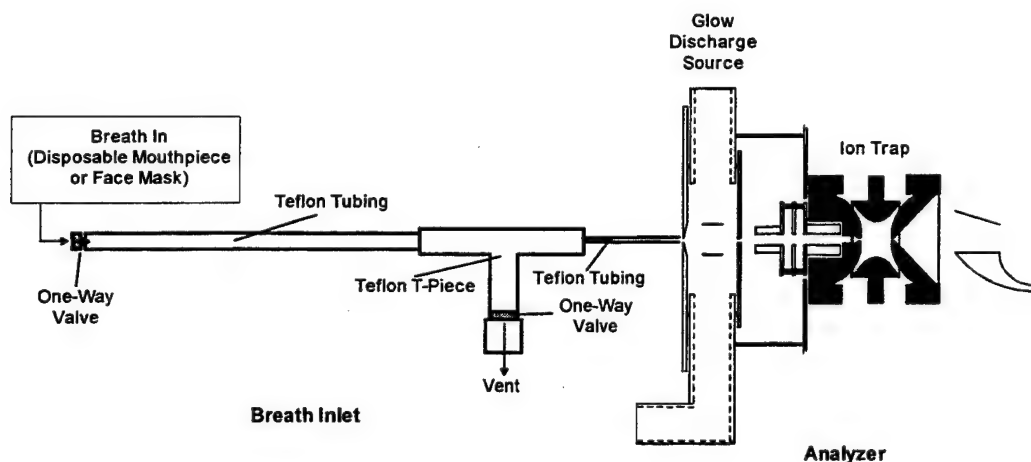


Figure 3-3. Continuous breath inlet system attached to direct breath sampling glow discharge source and ion trap mass spectrometer.

The volume of the breath inlet (in Figure 3-3) is 95 mL, or roughly the mean value of the adult tidal volume. Thus, each breath exhalation effectively displaces the previous breath sample, while a steady gas flow is maintained into the analyzer. This pragmatically ensures that unit resolution is achieved between individual breath exhalations while, at the same time, producing a constant and undiluted sample for analysis. A dry gas meter (Model DTM-115, American Meter Co.) was attached to the vent of the breath inlet system via wide-bore flexible tubing in order to record the total exhaled volume from each subject.

The direct breath sampling interface is a glow discharge ionization source, which is attached to the ITMS (Figure 3-3). The operation of this system has been described in detail elsewhere (McLuckey et al., 1988; McLuckey et al., 1989; Asano et al., 1990). The analyzer is a Teledyne Electronic Technologies (Mountain View, CA) 3DQ™ Discovery ion trap MS (Gordon et al., 1995). The 3DQ is a compact, field-deployable instrument with high sensitivity and specificity (Kelley et al., 1993; Kenny et al., 1993). Specificity for detection of 1,1,1-trichloroethane was further enhanced by operating the instrument in the MS/MS mode, in which the isolated precursor ions (at m/z 97) are dissociated and transformed into characteristic fragment ions (at m/z 61), with high conversion efficiency.

To calibrate the real-time breath analyzer, gas standards of the target compound were prepared in a 186-L glass chamber. Pure 1,1,1-trichloroethane was injected via a septum into humidified ultra-high purity air in the chamber at room temperature. A stainless steel fan in the chamber was used to mix the standard with the air. Whole air samples (6 L) were taken from the chamber in evacuated stainless steel canisters and analyzed independently using a modified EPA method, TO-14 (Winberry et al., 1990).

3.3 Data Processing

The total exposure E_x of each subject's left forearm and hand to the chemical in the chamber is given by the product of the steady-state exposure concentration C_{expos} and the total exposure time t_{expos} , i.e., $E_x = C_{expos} t_{expos}$.

The time-integrated area under the experimental breath expiration curve (e.g., Figure 4-1) provides a measure of the absorbed dose D_{br} . Multiplying D_{br} by the ventilation rate V_R yields the total mass of the chemical M_{br} that leaves the body by exhalation:

$$M_{br} = D_{br}V_R \quad (1)$$

In the present study, the absorbed dose is associated with dermal exposure of the left forearm and hand of each participant. The surface area SA of the exposed forearm and hand is assumed to be 10% of the total body surface area ($SA \approx 1,800 \text{ cm}^2$) (Corley et al., 1997). For a typical worker, we may reasonably assume that the head and neck, and both arms and hands can be exposed to solvent vapors, and this is assumed to correspond to 30% of the total body surface area.

If the blood/breath partition coefficient P_I is known ($P_I \approx 3$ for 1,1,1-trichloroethane) (Sato and Nakajima, 1987; Gargas et al., 1989; Wallace et al., 1997), the alveolar breath concentration can also be used to estimate the concentration of the compound in the blood C_{bl} at any time during the exposure (Lindstrom and Pleil, 1996):

$$C_{bl} = C_{br}P_I \quad (2)$$

SECTION 4.0 — Results

Multiple measurements of the exhaled breath concentration were made during and after forearm-and-hand exposure to vapors of 1,1,1-trichloroethane at 40°C. Each exposure sequence was preceded by a brief conditioning of the skin in either saline solution, untreated tap water, or heated room air. Figure 4-1 shows the breath 1,1,1-trichloroethane concentration/time profile obtained in this way for subject 2 (female) at a vapor concentration of 2,031 mg/m³ (1.06 x TLV) and temperature of 40°C following pre-conditioning of the forearm in warm room air by wrapping it in a heating pad at 40°C for 15 min (cf. Table 3-1). The plot shows that, after the start of dermal exposure to the vapor, the concentration of breath 1,1,1-trichloroethane rises quite quickly to 60—70 µg/m³ after about 33 min. Once the subject withdraws the forearm and hand from the chamber and exposure ceases, the breath level decreases. As shown in Figures 4-2 to 4-10, similar breath uptake/elimination plots were obtained for all the subjects under a variety of pre-exposure soak conditions.

In a preliminary experiment with a laboratory researcher as the subject, we showed that, without any preconditioning, the skin offers excellent protection against dermal absorption of the target chemical. Figure 4-11 presents the breath concentration/time plot obtained as the subject inserted his dry, untreated forearm and hand into the chamber, which already contained 1,1,1-trichloroethane at a vapor concentration of ~4,860 mg/m³ (~2.5 x TLV) and a temperature of 40°C. Exposure continued for a period of 14 min. For this experiment, the subject inhaled room air and exhaled into a disposable mouthpiece that was attached to the breath inlet system. Leakage of 1,1,1-trichloroethane from the chamber into the room resulted in brief inhalation exposure, which in turn gave rise to the large transient peak observed in Figure 4-11 at ~2 min. After returning to the starting level, the breath analyzer signal shows no increase in breath concentration as a result of dermal exposure to the vapor.

On the other hand, the plots in Figures 4-1 to 4-10 show clearly that pre-conditioning the forearm and hand in various soak media at 40°C leads to significant dermal absorption as a result of

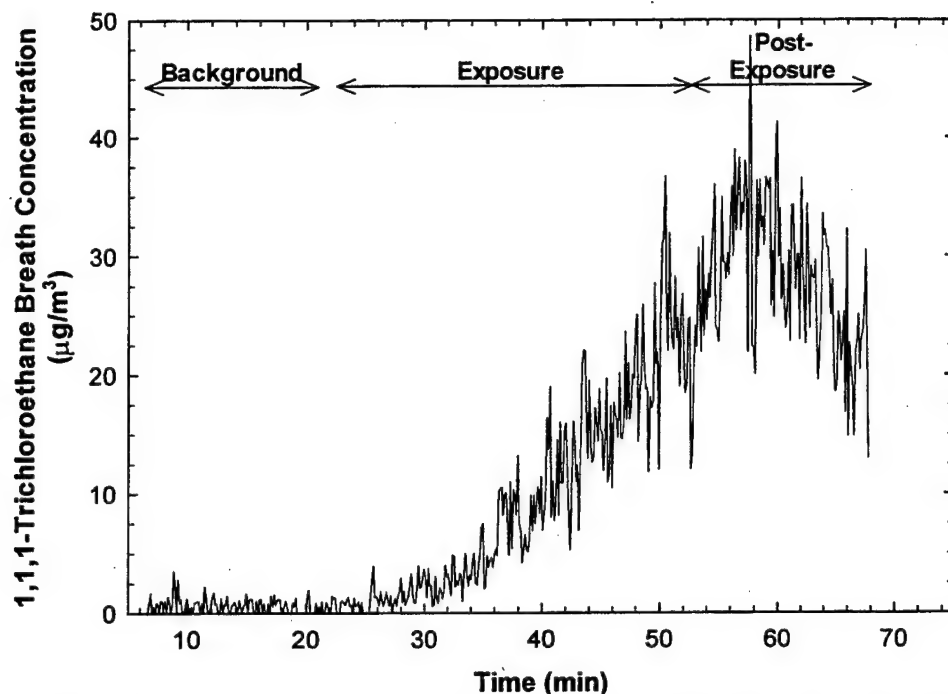


Figure 4-1. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 1 (male) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 1,205 mg/m^3 ; temperature: 40°C. Subject conditioned forearm and hand in saline solution at 40°C for 15 min before exposure.

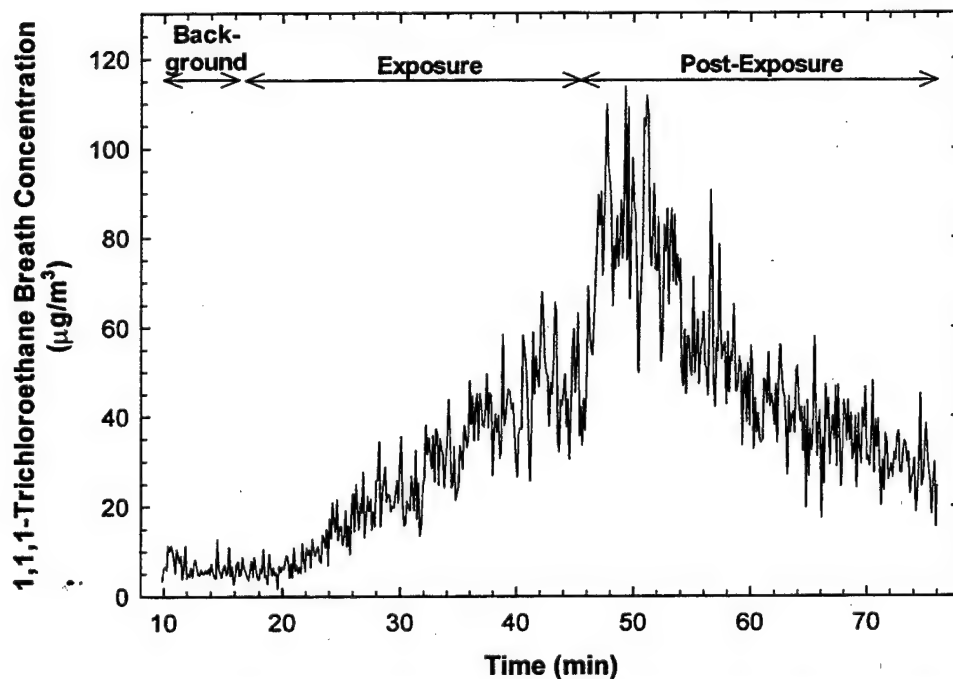


Figure 4-2. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 1 (male) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 1,878 mg/m^3 ; temperature: 40°C. Subject conditioned forearm and hand in saline solution at 40°C for 15 min before exposure.

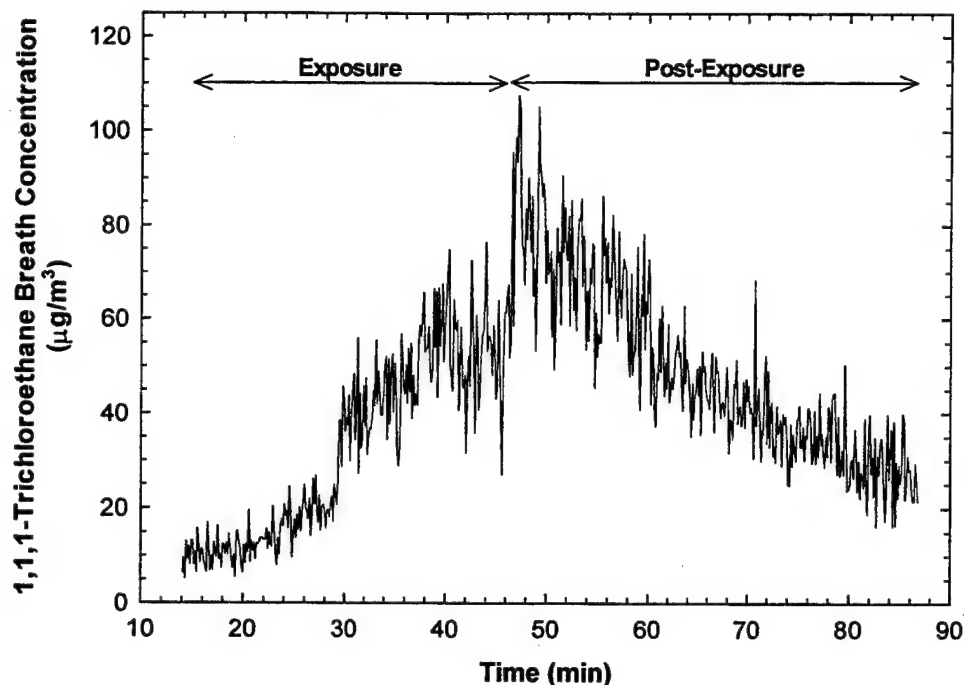


Figure 4-3. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 1 (male) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 2,118 mg/m³; temperature: 40°C. Subject conditioned forearm and hand in tap water at 40°C for 15 min before exposure.

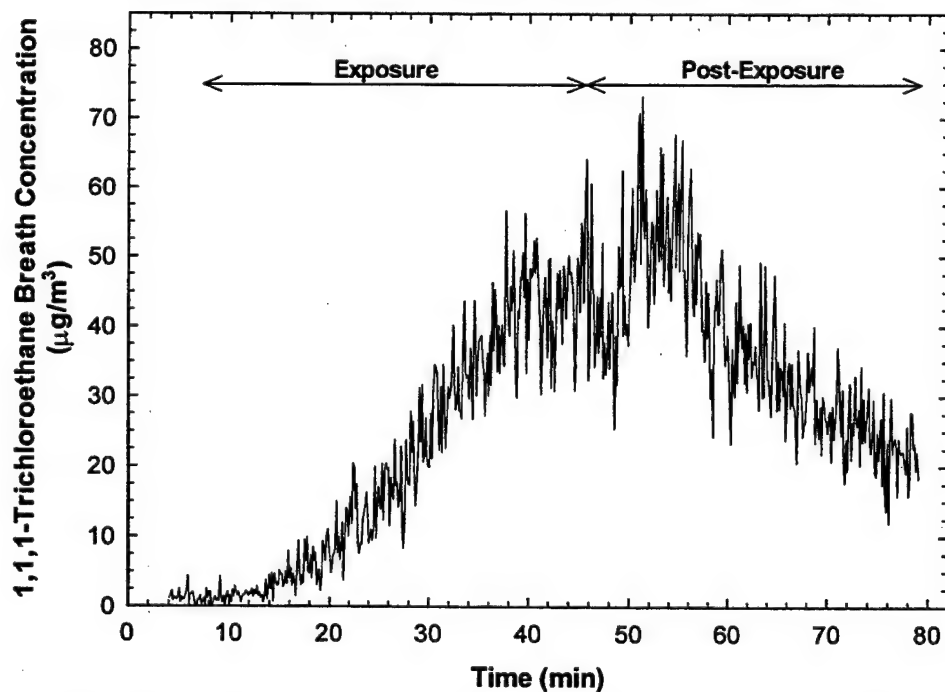


Figure 4-4. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 1 (male) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 2,083 mg/m³; temperature: 40°C. Subject conditioned forearm in room air at 40°C for 15 min before exposure.

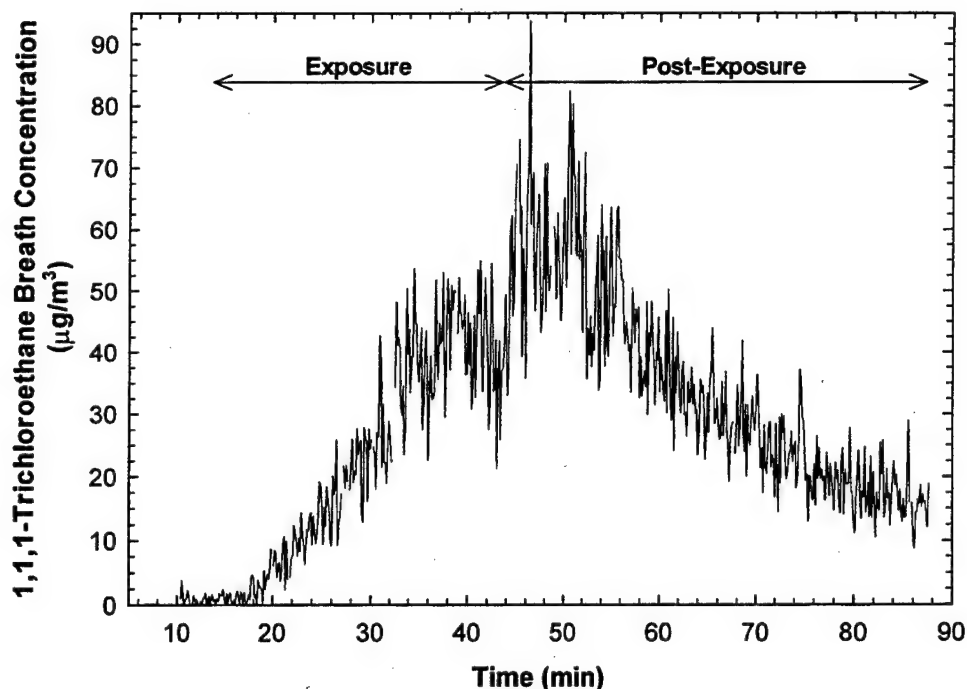


Figure 4-5. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 2 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 1,227 mg/m³; temperature: 40°C. Subject conditioned forearm and hand in saline solution at 40°C for 15 min before exposure.

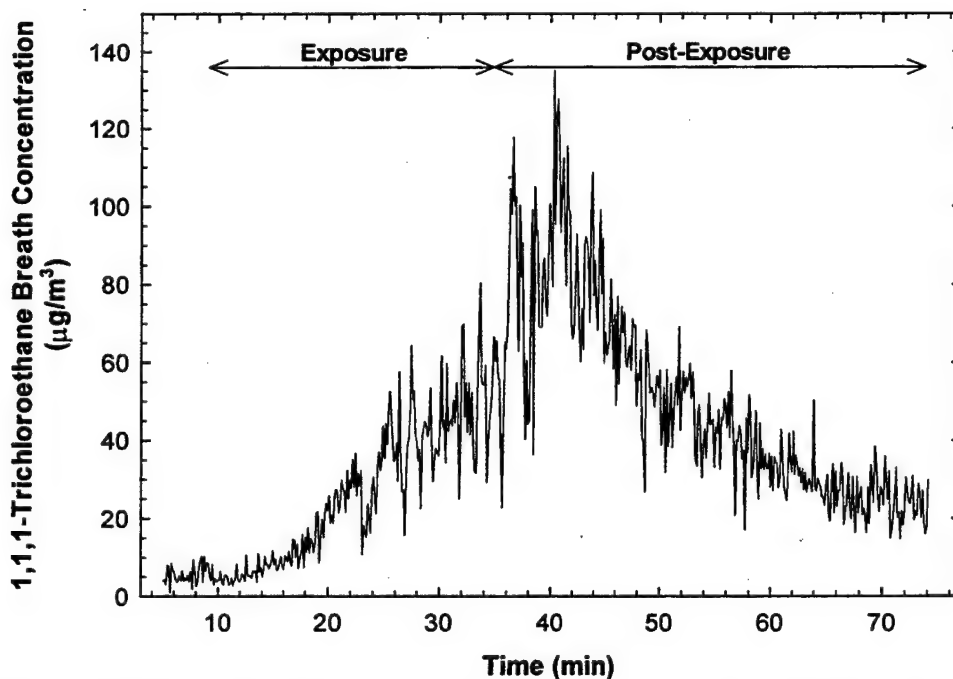


Figure 4-6. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 2 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 2,148 mg/m³; temperature: 40°C. Subject conditioned forearm and hand in saline solution at 40°C for 15 min before exposure.

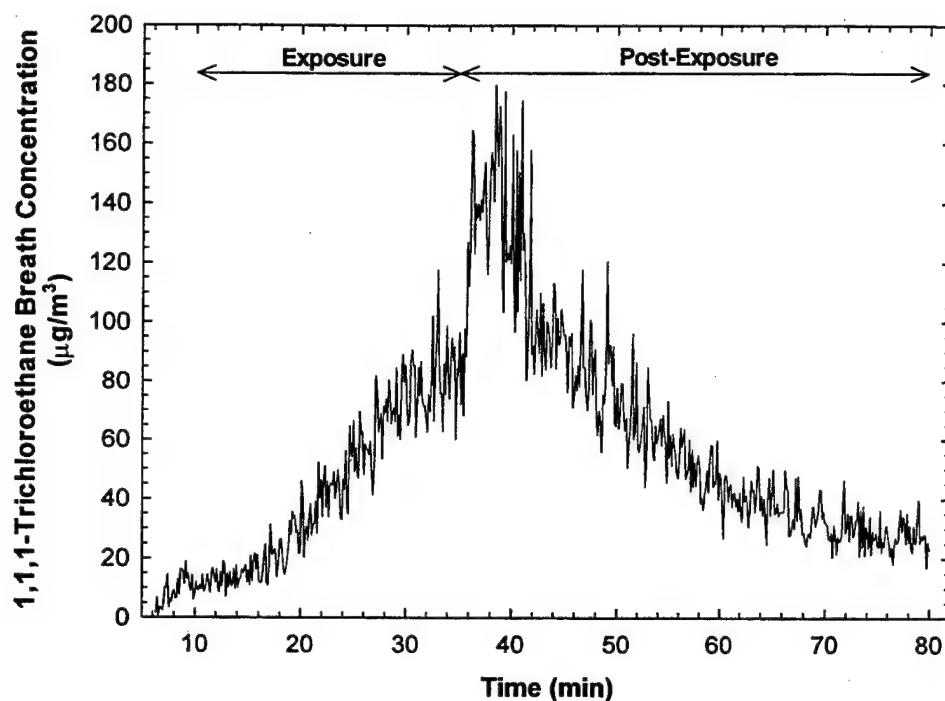


Figure 4-7. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 2 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 2,361 mg/m³; temperature: 40°C. Subject conditioned forearm and hand in tap water at 40°C for 15 min before exposure.

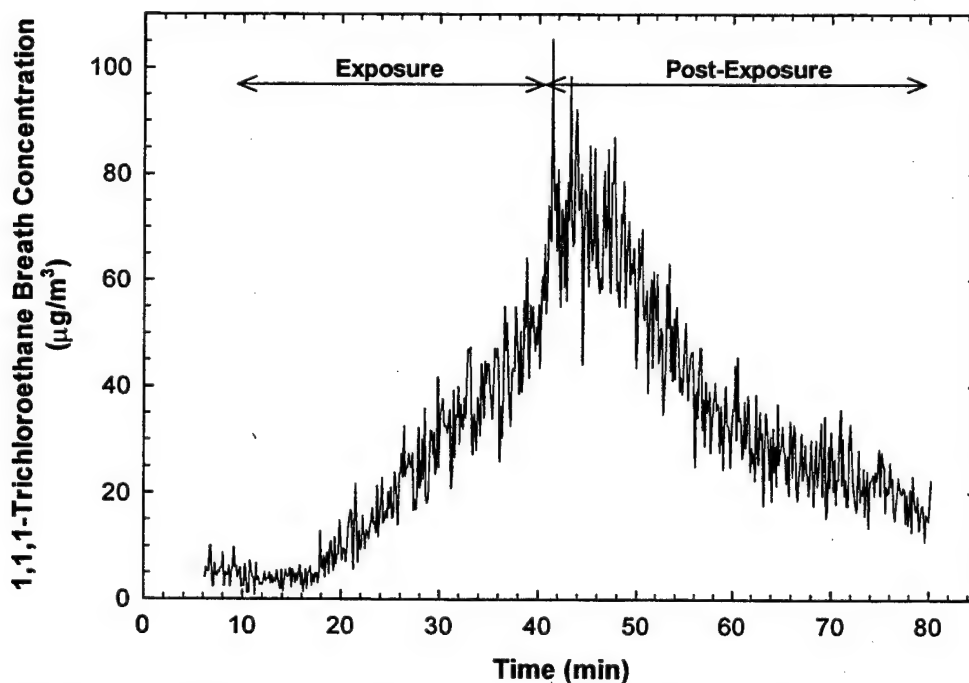


Figure 4-8. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 2 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: 2,031 mg/m³; temperature: 40°C. Subject conditioned forearm in room air at 40°C for 15 min before exposure.

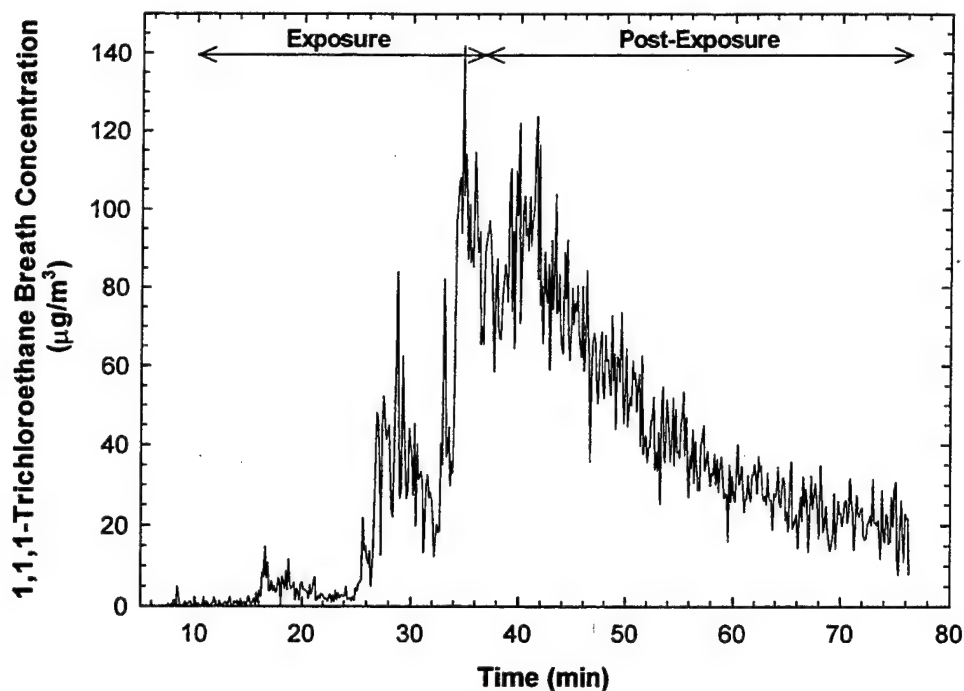


Figure 4-9. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 4 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: $2,238 \text{ mg}/\text{m}^3$; temperature: 40°C . Subject conditioned forearm and hand in saline solution at 30°C for 15 min before exposure.

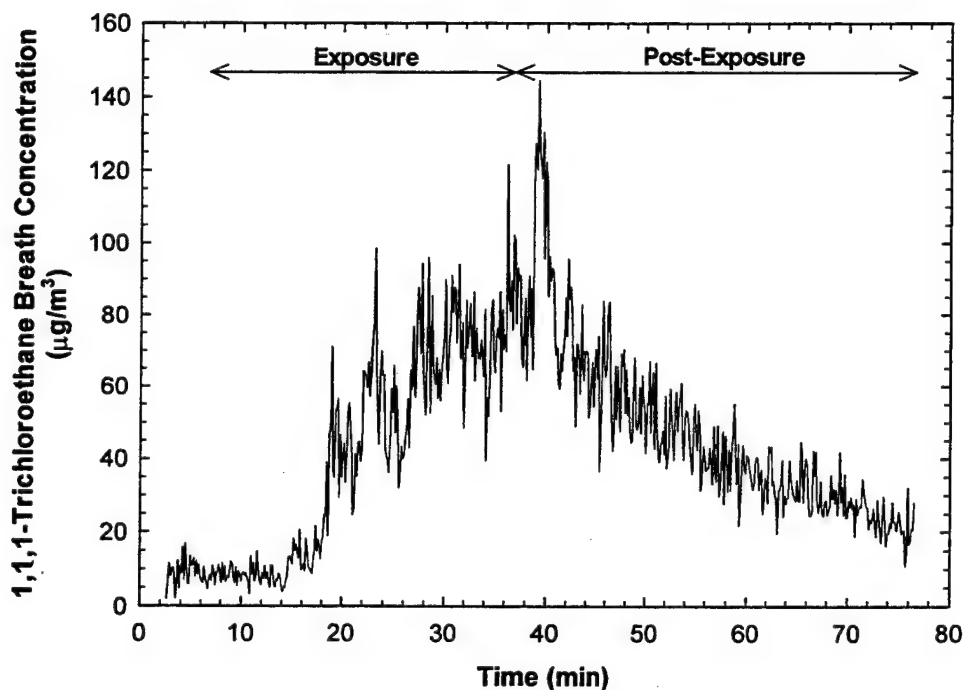


Figure 4-10. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for Subject 4 (female) during and after dermal exposure to vapors of 1,1,1-trichloroethane. Vapor concentration: $2,407 \text{ mg}/\text{m}^3$; temperature: 40°C . Subject conditioned forearm and hand in saline solution at 35°C for 15 min before exposure.

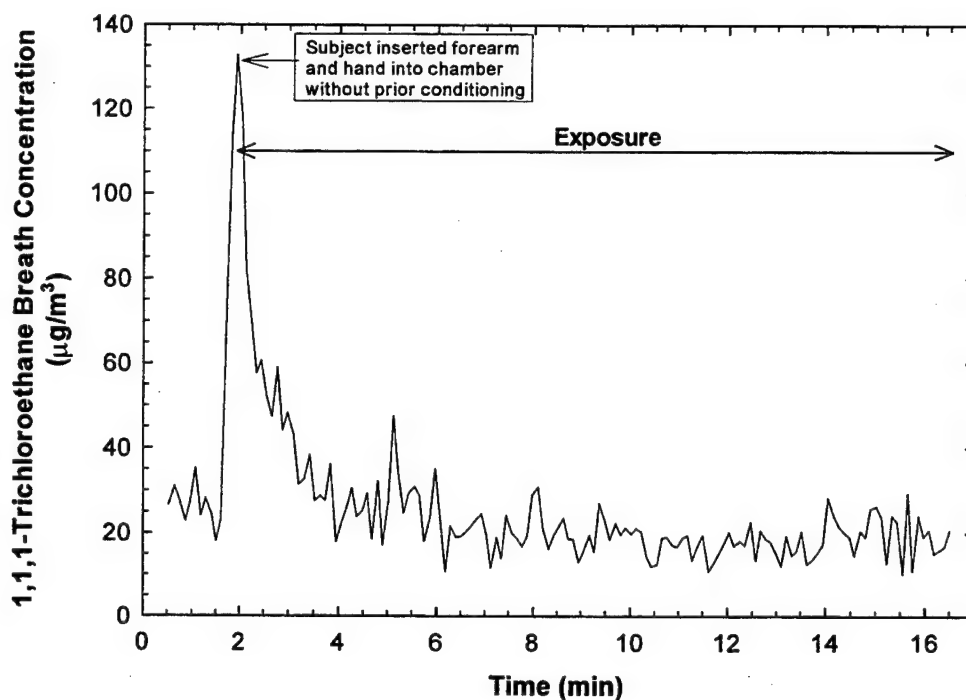


Figure 4-11. Continuous exhaled air concentration of 1,1,1-trichloroethane as a function of time for test subject during dermal exposure to vapors of 1,1,1-trichloroethane for a period of ~14 min. Vapor concentration was $\sim 4,860 \text{ mg}/\text{m}^3$ ($\sim 2.5 \times \text{TLV}$) at a temperature of 40°C . Subject inserted forearm and hand into chamber containing the test chemical without prior conditioning in saline, tap water, or heated room air. Subject inhaled room air and exhaled into disposable mouthpiece as he inserted his arm through the iris collar into the chamber containing the chemical. Leakage of chemical past forearm during insertion resulted in inhalation exposure, which caused the large, transient peak at ~2 min.

exposure to the solvent vapor. Moreover, the data in Figure 4-12 indicate a strong linear dependence of exhaled breath concentration on exposure vapor concentration, following a 15-min pre-soak in saline solution at 40°C . To determine the dependence of dermal absorption on the soak medium, we normalized all the breath levels measured at a target vapor concentration of ($1.0 \times \text{TLV}$) and temperature of 40°C , following a 15-min pre-soak in saline solution at 40°C . The results, which are shown in Figure 4-13, suggest that the exhaled breath concentration is essentially independent of the specific soak medium, when the skin of the forearm and hand are preconditioned at 40°C for a period of about 15 min prior to exposure.

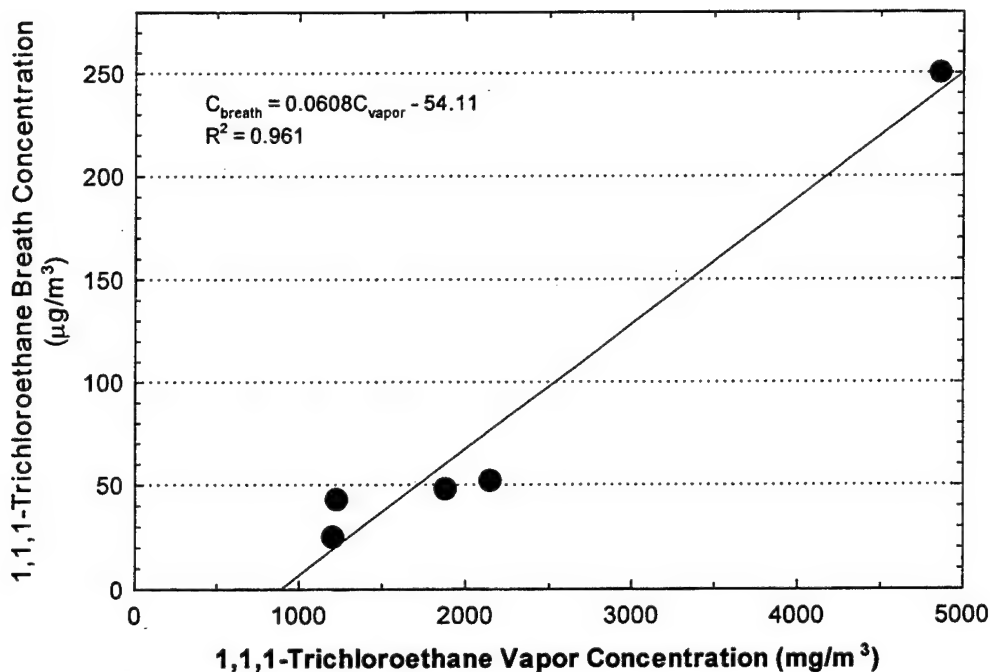


Figure 4-12. Effect of 1,1,1-trichloroethane vapor concentrations at 40°C on continuous exhaled air concentrations after subjects pre-soaked their forearms and hands in saline solution at a temperature of 40°C for periods of 15 min each.

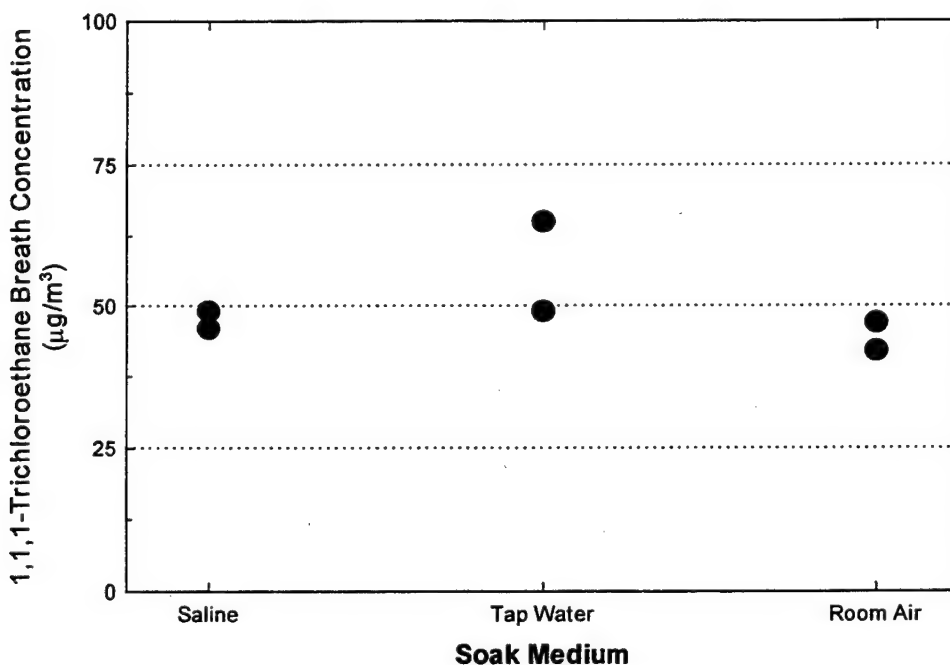


Figure 4-13. Effect of soak medium on continuous exhaled air concentrations of 1,1,1-trichloroethane vapor following dermal exposure to normalized vapor concentration of 1,910 mg/m³ (1.0 x TLV) at a temperature of 40°C after subjects conditioned their forearms and hands in saline, tap water, or room air at 40°C for periods of 15 min each.

The amount of 1,1,1-trichloroethane exhaled during the dermal uptake and decay periods was calculated by integrating the area under the breath concentration/time curve, using the trapezoidal rule (SigmaPlot 4.0 for Windows; SPSS, Inc.), and multiplying the result by the measured respiration rate for each experiment. Values obtained for all of the subjects are presented in Table 4-1. The mean amount of 1,1,1-trichloroethane exhaled under these conditions was $23.1 \pm 5.9 \mu\text{g}$ [mean \pm standard deviation].

The potential contribution of inhalation exposure to total absorbed dose, under the prevailing experimental conditions, can be estimated from the results of a recent chamber inhalation study (Wallace et al., 1997). Wallace et al. (1997) exposed five human subjects to several solvents, including 1,1,1-trichloroethane, at typical environmental concentrations ($800\text{--}10,500 \mu\text{g}/\text{m}^3$) and collected breath samples during a 10-h uptake phase and a 24-h decay phase. The distribution and residence times in the body were calculated using a linear four-compartment mass-balance model, viz.,

$$C_{br} = fC_{air} \sum a_i (1 - e^{-t/\tau_i}) \quad (t \leq T) \quad (3)$$

$$C_{br} = fC_{air} \sum a_i (1 - e^{-t/\tau_i}) e^{-(t-T)/\tau_i} \quad (t \geq T) \quad (4)$$

where C_{br} = exhaled breath concentration; C_{air} = chamber air concentration; f = fraction of inhaled breath concentration exhaled at equilibrium; a_i = fractional contribution of the i^{th} compartment to the breath at equilibrium ($\sum a_i = 1$); t = time from start of exposure; T = time of exposure to a constant concentration C_{air} ; and τ_i = residence time of chemical in the i^{th} compartment. For 1,1,1-trichloroethane, the experiments conducted by Wallace et al. (1997) provided the following values for the parameters in Equations (3) and (4):

$$a_1 = 0.21$$

$$a_2 = 0.24$$

$$a_3 = 0.19$$

$$a_4 = 0.31$$

$$\tau_1 = 0.15 \text{ h}$$

Table 4-1. Exhaled Dose for Subjects Dermally Exposed to 1,1,1-Trichloroethane Vapor

Subject	Pre-Exposure Conditioning	Chamber Vapor Conc., C_{expos} (mg/m ³)	Exposure Time (min)	Post-Exposure Time (min)	Total Normalized AUC, ^a E_x (μg·min/m ³)	Total Exhaled Volume (m ³)	Measured Respiration Rate, V_R (L/min)	Exhaled Dose, M_{br} (μg)
1	Saline soak at 40°C	1,205	30.4	15.3	1391	0.587	12.8	17.8
	Saline soak at 40°C	1,878	28.6	30.4	2604	0.671	11.4	29.7
	Tap water soak at 40°C	2,118	31.4	40.8	2942	0.460	6.4	18.8
	Room air soak at 40°C	2,083	38.7	33.4	2083	1.050	14.5	30.2
2	Saline soak at 40°C	1,227	30.1	43.9	1924	0.509	6.9	13.2
	Saline soak at 40°C	2,148	26.0	39.1	2751	0.509	7.8	21.5
	Tap water soak at 40°C	2,361	25.3	44.7	3666	0.511	7.3	26.8
	Room air soak at 40°C	2,031	30.7	39.3	2257	0.572	8.2	18.5
4	Saline soak at 30°C	2,238	26.1	40.1	2463	0.718	10.8	26.6
	Saline soak at 35°C	2,407	30.3	39.9	3103	0.632	9.0	27.9

^a AUC = area under curve; areas corresponding to exposure and post-exposure periods normalized to 30 min and 40 min, respectively.

$$\tau_2 = 0.68 \text{ h}$$

$$\tau_3 = 4.8 \text{ h}$$

$$\tau_1 = 29 \text{ h}$$

$$f = 0.875$$

Substituting the values for these parameters into Equations (3) and (4), we first calculated the value of the ratio C_{br}/fC_{air} as a function of time t , for an exposure period $T = 30$ min, and a post-exposure period of 40 min. The resulting inhalation uptake and decay curve is shown in Figure 4-14.

We assumed that the model developed by Wallace et al. (1997) for inhalation exposure to 1,1,1-trichloroethane can be applied at the much higher chamber air concentrations used in the present study (1,205—2,407 mg/m³), and used it to calculate the uptake (over a 30 min period) and decay (over a 40 min period) in the breath of the same subjects if they had been exposed to the

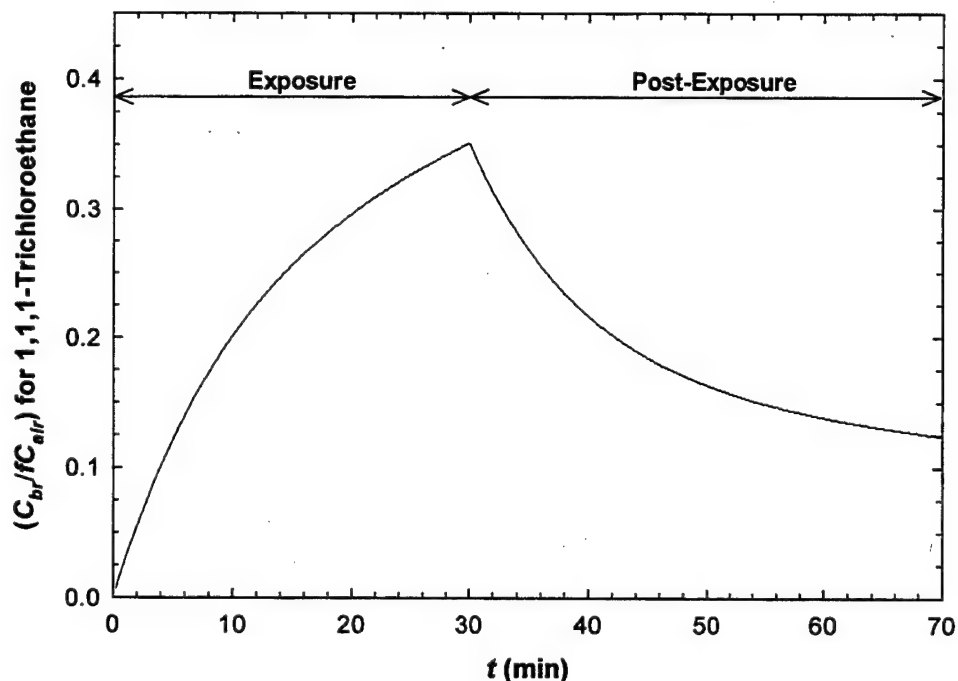


Figure 4-14. Variation of C_{br}/fC_{air} as a function of time t for inhalation exposure to 1,1,1-trichloroethane, from Equations (3) and (4) and parameters determined by Wallace et al. (1997). Exposure (uptake) period $T = 30$ min and post-exposure (decay) period = 40 min.

chemical without protective respiratory equipment at these concentrations. As before, the predicted amount of 1,1,1-trichloroethane exhaled during the inhalation exposure and post-exposure periods was calculated by integrating the area under each breath concentration/time curve obtained from the model and multiplying the result by the measured respiration rate for the subject in each experiment. The results are summarized in Table 4-2, where the exhaled dose due to inhalation exposure is compared with the exhaled dose resulting from dermal absorption over 30% of the total body surface area.

Table 4-2. Comparison of Exhaled Dose Following Dermal and Inhalation Exposure to 1,1,1-Trichloroethane Vapors

Subject	Pre-Exposure Conditioning	Vapor Conc., C_{expos} (mg/m ³)	Exhaled Dose (μg)		Dermal Contribution (as % of Inhalation Component)
			From Dermal Uptake of Vapor ^a	From Inhalation Uptake of Vapor ^b	
1	Saline soak at 40°C	1,205	53.4	1.93 x 10 ⁵	0.028
	Saline soak at 40°C	1,878	89.1	2.68 x 10 ⁵	0.033
	Tap water soak at 40°C	2,118	56.5	1.70 x 10 ⁵	0.033
	Room air soak at 40°C	2,083	90.6	3.78 x 10 ⁵	0.024
2	Saline soak at 40°C	1,227	39.8	1.06 x 10 ⁵	0.038
	Saline soak at 40°C	2,148	64.4	2.10 x 10 ⁵	0.031
	Tap water soak at 40°C	2,361	80.3	2.16 x 10 ⁵	0.037
	Room air soak at 40°C	2,031	55.5	2.08 x 10 ⁵	0.027
4	Saline soak at 30°C	2,238	79.8	3.02 x 10 ⁵	0.026
	Saline soak at 35°C	2,407	83.8	2.71 x 10 ⁵	0.031

^a Exhaled dose calculated assuming that dermal absorption occurs over 30% of the total body surface area.

^b Calculated using model and parameters for 1,1,1-trichloroethane obtained from chamber inhalation exposure study conducted by Wallace et al. (1997).

SECTION 5.0 — Discussion

This study has demonstrated that normal untreated skin provides an excellent barrier to the dermal uptake of a solvent vapor such as 1,1,1-trichloroethane. Warm and/or moist skin, on the other hand, has been shown to promote skin permeability to 1,1,1-trichloroethane vapors. Previous studies in humans of the dermal absorption of solvents from the vapor phase did not investigate this dependence (Riihimäki and Pfäffli, 1978; Brooke et al., 1998).

A second striking result of these studies is the strong linear dependence of exhaled breath concentration on 1,1,1-trichloroethane vapor concentration at 40°C, following skin pre-conditioning in physiological saline solution at 40°C for a period of 15 min (Figure 4-12). This indicates that, over the exposure range used (~1,200—4,800 mg/m³), dermal uptake is a direct function of vapor concentration.

Further investigation showed that, for a fixed solvent vapor concentration, vapor temperature, and pre-conditioning temperature, the exhaled breath concentration is essentially independent of the specific soak medium used (saline, tap water, or room air), at the vapor and soak temperatures used (Figure 4-13). In one of the early test experiments we conducted, the soak medium (room air) was held at room temperature (~25°C) and no increase in breath concentration was observed. However, for soak-medium temperatures between 30 and 40°C, we found that the breath concentration was largely unaffected by soak-medium temperature, for a fixed solvent vapor concentration, vapor temperature, and soak medium (saline).

The estimates of dermal uptake of 1,1,1-trichloroethane vapors in the present study were compared with the predicted contributions of inhalation uptake, under the same experimental conditions, using the results of a recent chamber inhalation study conducted by Wallace et al. (1997). From the estimates made in the current study, we conclude that dermal uptake (from assumed exposure over 30% of the total body surface area) as a fraction of inhalation exposure (in the absence of any respiratory protection) is an average of $0.031 \pm 0.005\%$. This suggests that the contribution of dermal uptake of 1,1,1-trichloroethane vapors to total absorbed dose is negligible compared with the inhalation component. In a similar study of exposure to 1,1,1-

trichloroethane vapors in humans, Riihimäki and Pfäffli (1978) investigated the dermal uptake of several solvent vapors. They estimated that the dermal uptake of 1,1,1-trichloroethane is ~0.1% of the inhalation uptake and found, in addition, that tetrachloroethylene and the aromatic solvents, xylene, styrene, and toluene, appear to be absorbed much more readily by human skin than 1,1,1-trichloroethane. Given that their measurements of dermal absorption were based on whole body exposure, as opposed to the forearm-and-hand-only exposure procedure used in the current study, our results for 1,1,1-trichloroethane are in good agreement with their estimate.

SECTION 6.0 — Conclusions and Recommendations

This study was conducted using newly-developed breath monitoring technology to determine the vapor phase uptake by humans of 1,1,1-trichloroethane by dermal absorption under exposure conditions that may reasonably be encountered by U.S. Air Force or other workers performing similar operations. Levels of 1,1,1-trichloroethane were monitored continuously in real time as dermal vapor exposure to the chemical took place following pre-conditioning of the exposed skin in heated saline solution, heated tap water, or heated room air.

The study showed that normal untreated skin provides an excellent barrier to the dermal uptake of a solvent vapor such as 1,1,1-trichloroethane. Warm and/or moist skin, on the other hand, was found to promote skin permeability to 1,1,1-trichloroethane vapors. The study also showed a strong linear dependence of exhaled breath concentration on 1,1,1-trichloroethane vapor concentration at 40°C, following skin pre-conditioning in physiological saline solution at 40°C for a period of 15 min. This indicates that, over the exposure range used (~1,200—4,800 mg/m³), dermal uptake is a direct function of vapor concentration.

Further investigation showed that, for a fixed solvent vapor concentration, vapor temperature, and pre-conditioning temperature, the exhaled breath concentration is essentially independent of the specific soak medium used (saline, tap water, or room air), at the vapor and soak temperatures used. In one of the early test experiments we conducted, the soak medium (room air) was held at room temperature (~25°C) and no clear increase in breath concentration was observed. However, for soak-medium temperatures between 30 and 40°C, the breath concentration was largely unaffected by soak-medium temperature, for a fixed solvent vapor concentration, vapor temperature, and soak medium (saline).

Measured values of the dermal uptake of 1,1,1-trichloroethane vapors were compared with predicted contributions due to inhalation uptake, under the same experimental conditions, using the results of a recent chamber inhalation study. From these estimates, dermal uptake (from assumed exposure over 30% of the total body surface area) as a fraction of inhalation exposure (in the absence of any respiratory protection) was estimated to be an average of $0.031 \pm 0.005\%$.

This suggests that the contribution of dermal uptake of 1,1,1-trichloroethane vapors to total absorbed dose is negligible compared with the inhalation component.

There are indications in the published literature that, for certain chemicals, absorption of vapors through the skin may represent a much larger fraction of the total uptake than is the case with 1,1,1-trichloroethane (Riihimäki and Pfäffli, 1978; Corley et al., 1997; Brooke et al., 1998). We therefore recommend that additional studies be conducted to determine the significance of this effect in several other polar and nonpolar chemicals that are of concern to the USAF.

SECTION 7.0 — References

- Andelman, J.B.: Human Exposures to Volatile Halogenated Organic Chemicals in Indoor and Outdoor Air. *Environ. Health Perspect.* 62:313-318 (1985).
- Asano, K.G.; McLuckey, S.A.; Glish, G.L.: Comparison of Atmospheric Sampling Glow Discharge Ionization with Electron Ionization. *Spectroscopy* 8:191-209 (1990).
- Brooke, I.; Cocker, J.; Delic, J.I.; et al.: Dermal Uptake of Solvents From the Vapour Phase: An Experimental Study in Humans. *Ann. Occup. Hyg.* 42:531-540 (1998).
- Corley, R.A.; Markham, D.A.; Banks, C.; et al.: Physiologically Based Pharmacokinetics and the Dermal Absorption of 2-Butoxyethanol Vapor by Humans. *Fundam. Appl. Toxicol.* 39:120-130 (1997).
- Cox, L.A.: Simple Relations Between Administered and Internal Doses in Compartmental Flow Models. *Risk Anal.* 15:197-204 (1995).
- Gargas, M.L.; Burgess, R.J.; Voisard, D.E.; et al.: Partition Coefficients of Low-Molecular-Weight Volatile Chemicals in Various Liquids and Tissues. *Toxicol. Appl. Pharmacol.* 98:87-99 (1989).
- Giardino, N.J.; Andelman, J.B.: Characterization of the Emissions of Trichloroethylene, Chloroform, and 1,2-Dibromo-3-chloropropane in a Full-Size, Experimental Shower. *J. Expos. Anal. Environ. Epidemiol.* 6:413-423 (1996).
- Giardino, N.J.; Wireman, J.R.: Total Body Burden from Inhalation During Showering with Benzene-Contaminated Drinking Water: Implications for Cancer Risk. *J. Hazardous Materials* 62:35-40 (1998).
- Gordon, S.M.; Kenny, D.V.; Kelly, T.J.: Continuous Real Time Breath Analysis for the Measurement of Half Lives of Expired Volatile Organic Compounds. *J. Expos. Anal. Environ. Epidemiol. Suppl.* 1:41-54 (1992).

Gordon, S.M.; Callahan, P.J.; Kenny, D.V.; et al.: Direct Trace Analysis of Volatile Organic Compounds in Air Using Ion Trap Mass Spectrometers with Filtered Noise Fields. In: Proceedings of the 1995 EPA/A&WMA International Symposium on Field Screening Methods for Hazardous Wastes and Toxic Chemicals, Vol. 1, pp. 670-679. VIP-47; Air & Waste Management Association, Pittsburgh (1995).

Gordon, S.M.; Wallace, L.A.; Callahan, P.J.; et al.: Effect of Water Temperature on Dermal Exposure to Chloroform. *Environ. Health Perspect.* 106:337-345 (1998).

Grandjean, P.: Skin penetration: Hazardous chemicals at work. Taylor and Francis, London (1990).

Jepson, G.W.; McDougal, J.N.: Physiologically Based Modeling of Nonsteady State Dermal Absorption of Halogenated Methanes From an Aqueous Solution. *Toxicol. Appl. Pharmacol.* 144:315-324 (1997).

Jo, W.K.; Weisel, C.P.; Liou, P.J.: Routes of Chloroform Exposure and Body Burden from Showering with Contaminated Tap Water. *Risk Anal.* 10:575-580 (1990).

Johanson, G.; Boman, A.: Percutaneous Absorption of 2-Butoxyethanol Vapour in Human Subjects. *Brit. J. Ind. Med.* 48:788-792 (1991).

Kelly, T.J.; Kenny, D.V.; Spicer, C.W.; et al.: Continuous Analysis of Human Breath Using Atmospheric Pressure Ionization MS/MS with a Novel Inlet Design. In: Proceedings of the 1989 U.S. EPA/A&WMA International Symposium on Measurement of Toxic and Related Air Pollutants, pp. 478-483. VIP-13, Air & Waste Management Association, Pittsburgh (1989); U.S. Patent 5,042,501, August 27, 1991.

Kenny, D.V.; Callahan, P.J.; Gordon, S.M.; et al.: Simultaneous Isolation of Two Different m/z Ions in an Ion Trap Mass Spectrometer and Their Tandem Mass Spectra Using Filtered Noise Fields. *Rapid Commun. Mass Spectrom.* 7:1086-1089 (1993).

Lindstrom, A.B.; Pleil, J.D.: A Methodological Approach for Exposure Assessment Studies in Residences Using Volatile Organic Compound—Contaminated Water. *J. Air & Waste Manage. Assoc.* 46:1058-1066 (1996).

McDougal, J.N.; Jepson, G.W.; Clewell III, H.J.; et al.: A Physiologically-Based Pharmacokinetic Model for Dermal Absorption of Vapors in the Rat. *Toxicol. Appl. Pharmacol.* 85:286-294 (1986).

McDougal, J.N.; Jepson, G.W.; Clewell III, H.J.; et al.: Dermal Absorption of Organic Chemical Vapors in Rats and Humans. *Fundam. Appl. Toxicol.* 14:299-308 (1990).

McLuckey, S.A.; Glush, G.L.; Asano, K.G.; et al.: Atmospheric Sampling Glow Discharge Ionization Source for the Determination of Trace Organic Compounds in Ambient Air. *Anal. Chem.* 60:2220-2227 (1988).

McLuckey, S.A.; Glush, G.L.; Asano, K.G.: The Coupling of an Atmospheric Sampling Ion Source with an Ion Trap Mass Spectrometer. *Anal. Chim. Acta* 225:25-35 (1989).

Meuling, W.J.; Franssen, A.C.; Brouwer, D.H.; et al.: The Influence of Skin Moisture on the Dermal Absorption of Propoxur in Human Volunteers: A Consideration for Biological Monitoring Practices. *Sci. Total Environ.* 199:165-172 (1997).

Raymer, J.H.; Pellizzari, E.D.; Thomas, K.W.; et al.: Elimination of Volatile Organic Compounds in Breath After Exposure to Occupational and Environmental Microenvironments. *J. Expos. Anal. Environ. Epidemiol.* 1:439-451 (1991).

Riihimäki, V.; Pfaffli, P.: Percutaneous Absorption of Solvent Vapors in Man. *Scand. J. Work Environ. Health* 4:73-85 (1978).

Sato, A.; Nakajima, T.: Pharmacokinetics of Organic Solvent Vapors in Relation to Their Toxicity. *Scand. J. Work Environ. Health* 13:81-93 (1987).

Wallace, L.A.; Pellizzari, E.D.; Gordon, S.M.: A Linear Model Relating Breath Concentrations to Environmental Exposures: Application to a Chamber Study of Four Volunteers Exposed to Volatile Organic Chemicals. *J. Expos. Anal. Environ. Epidemiol.* 3:75-102 (1993).

Wallace, L.A.; Buckley, T.; Pellizzari, E.; et al.: Breath Measurements as Volatile Organic Compound Biomarkers. *Environ. Health Perspect.* 104 (Suppl. 5):861-869 (1996).

Wallace, L.A.; Nelson, W.C.; Pellizzari, E.D.; et al.: Uptake and Decay of Volatile Organic Compounds at Environmental Concentrations: Application of a Four-Compartment Model to a Chamber Study of Five Human Subjects. *J. Expos. Anal. Environ. Epidemiol.* 7:141-163 (1997).

Weisel, C.P.; Jo, W.K.; Liou, P.J.: Utilization of Breath Analysis for Exposure and Dose Estimates of Chloroform. *J. Expos. Anal. Environ. Epidemiol. Suppl.* 1:55-69 (1992).

Weisel, C.P.; Jo, W.K.: Ingestion, Inhalation, and Dermal Exposures to Chloroform and Trichloroethene from Tap Water. *Environ. Health Perspect.* 104:48-51 (1996).

Wester, R.C.; Maibach, H.I.: Percutaneous Absorption of Chemicals from Water Simulating Swimming and Bathing and from Vapor Exposure. In: *Environ. Sci. Pollut. Control Ser. 9 (Water Contamination and Health)*, pp. 149-165 (1994).

Wilkes, C.R.; Small, M.J.; Davidson, C.I.; et al.: Modeling the Effects of Water Usage and Co-Behavior on Inhalation Exposures to Contaminants Volatilized from Household Water. *J. Expos. Anal. Environ. Epidemiol.* 6:393-412 (1996).

Winberry Jr, W.T.; Murphy, N.T.; Riggin, R.M.: *Methods for Determination of Toxic Organic Compounds in Air: EPA Methods.* Noyes Data Corporation, Park Ridge, NJ (1990).